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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/897,107	07/03/2001	Akihiko Yamagishi	210383US0	9251

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EXAMINER

RAMIREZ, DELIA M

ART UNIT PAPER NUMBER

1652

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/897,107

Applicant(s)

YAMAGISHI, AKIHIKO

Examiner

Delia M. Ramirez

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 January 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 17, 19, 20, 23, 27 and 28 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 17, 19, 20, 23, 27 and 28 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: PIR definition

DETAILED ACTION

Status of the Application

Claims 17, 19-20, 23, 27 and 28 are pending.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/26/2004 has been entered.

Applicant's cancellation of claims 18, 21-22, 24-26, amendment of claims 17, 23, amendments to the abstract and the specification, and addition of claims 27-28 in a communication filed on 1/26/2004 are acknowledged.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

1. Claims 17 and 23 are objected to due to the recitation of "method and said proteins include proteins from the species selected from the group..". For clarity, it is suggested that the term be replaced with "method, wherein said proteins include proteins from species selected from the group...".

Appropriate correction is required.

2. Claims 17 and 23 are objected to due to the recitation of "(iii) comparing....the amino acid sequence in one of the proteins compared..". For clarity, it is suggested that the term be replaced with "(iii) comparing....the amino acid sequence of one of the proteins compared..". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 17, 19-20, 23, 27 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claims 17 and 23 (claims 19-20 and 28 dependent thereon) are indefinite in the recitation of “proteins belonging to the same family that are similar to each other in at least one of the features selected from the group consisting of function, amino acid sequence, domain structure and steric structure” for the following reasons. The term “similar” is a relative term and neither the claims nor the specification provide a standard for ascertaining the requisite degree. As such, one cannot reasonably determine which proteins are being used in step (i), particularly in view of the fact that there is no clue in the specification as to what constitute “similar” as it relates to an amino acid sequence, domain structure or steric structure. For example, in the case of amino acid sequence, there is no indication as to which % identity would constitute “similar”. For examination purposes, it will be assumed that the term “proteins belonging to the same family that are similar to each other in at least one of the features selected from the group consisting of function, amino acid sequence, domain structure and steric structure” refers to proteins of similar biochemical function that are more than 50% sequence identical as defined by Dayhoff et al. (1978) and used by the Protein Information Resource (PIR). See attached definition. No patentable weight will be given to the term “amino acid sequence, domain structure and steric structure”.

Correction is required.

6. Claims 17 and 23 (claims 19-20, 27 and 28 dependent thereon) are indefinite in the recitation of “comparing amino acid sequences of proteins belonging to the same family that are similar to each other in at least one of the features selected from....domain structure and steric structure and deriving from two

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or more species, wherein said proteins evolutionarily correspond to each other in a phylogenic tree..." for the following reasons. The term "and deriving from two or more species" is unclear since one cannot determine what is deriving from two or more species. If the term refers to the proteins whose amino acid sequences are being compared, it is suggested that the term be amended to recite "wherein said proteins derive from two or more species" or "wherein said proteins are isolated from two or more species".

As indicated in the previous Office Action, the term "wherein said proteins evolutionarily correspond to each other in a phylogenic tree" is unclear and confusing. Applicants argue that the specification in pages 6-10 provide a detailed discussion of how the proteins correspond to one another on an evolutionary basis. Furthermore, Applicants indicate that proteins derived from two or more species correspond to each other when these proteins appear at the similar location in the phylogenic tree designated for each individual species. Applicant's arguments have been considered but are not found persuasive. While it is agreed that those pages of the specification disclose how to find the ancestral protein, the Examiner disagrees with Applicant's contention that this section of the specification shows the intended meaning of the term, or that it is clear that proteins derived from two or more species correspond to each other when these proteins appear at a similar location in the phylogenic tree designed for each individual species. It is noted that based on the specification, a phylogenic tree is a diagram indicating the evolutionary relationship among different organisms based on, for example 16S rRNA or in this case, proteins of some known function. In the instant case, a phylogenic tree is designed using the amino acid sequence of proteins such as ICDH or IPMDH, which are proteins which have related enzymatic activity. Since the term "species" appears to be equivalent to "organisms", it is unclear as to how a phylogenic tree can be designed for an individual "organism" or what is a phylogenic tree designed for an "organism". As such, one cannot determine what are proteins which evolutionarily correspond to each other in a phylogenic tree. The specification does not provide a specific definition of the term or even an example to clarify the term. It is reiterated herein that one cannot determine if the term refers to

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(1) proteins which have a similar biological function, similar structure or both, or (2) whether the term is also limiting the organisms from which such proteins are isolated based on their position in a phylogenetic tree. It is suggested that Applicants amend the claim to clearly indicate the intended limitation, provide clarification of the term, or provide an example/diagram/reference which would allow the Examiner to understand the meaning of the term. For examination purposes, it will be assumed that the term “wherein said proteins evolutionarily correspond to each other in a phylogenetic tree” refers to “proteins derived from organisms evolutionarily related in a phylogenetic tree, wherein said proteins belong to the same general class of proteins”. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 17, 19-20, and 23 were rejected under 35 U.S.C. 112, first paragraph for introducing new matter.

9. Applicants submit that support for the term “proteins belonging to the same family” is found in page 5 of the specification. Applicant’s arguments have been found persuasive. Thus, this rejection is hereby withdrawn.

10. Claims 17 and 23 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

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11. This rejection has been discussed at length in Paper No. 17 (mailed on 8/26/2003) and Paper No. 12 (mailed on 12/18/2002), and it is applied to amended claims 17 and 23 for the reasons of record and those set forth below.

12. Applicant argue that the term "proteins belonging to the same family", as described in the specification, clearly indicates that the proteins to be compared are similar to each other either in function, amino acid sequence, domain structure, or steric structure. Furthermore, Applicants submit that that pages 5-6 and Example 1 of the specification provide that "information of amino acid sequences of proteins corresponding to each other..". Applicants also submit that the claims are now limited in regard to the methods for the construction of the phylogenic tree and that the teachings of the specification in pages 4-5 make it clear to one of skill in the art that proteins derived from two or more species correspond to each other when these proteins appear at the similar location in the phylogenic tree designed for each individual species.

13. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. The Examiner acknowledges the teachings of the specification and the amendments made to the claims, and agrees that the claims are now limited in regard to the methods used in the preparation of the phylogenic tree and that the term "proteins belonging to the same family" further limit the proteins whose amino acid sequences are used in the method. See Claim Rejections under 35 USC 112, second paragraph for claim interpretation. However, it is noted that the claims are still directed to a method for improving thermostability of proteins of any function. As indicated in previous Office Action Paper No. 17, to adequately describe a method for improving thermostability of proteins of any function, one of skill in the art would require disclosure of the amino acid sequences of those functional/structural homologs which are required to construct the ancestral protein. Furthermore, one would also require disclosure of those proteins (i.e. function) which can have their thermal stability enhanced. While one would expect proteins from thermophilic organisms to be thermally stable, this may not be the case for proteins of any

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function from non-thermophilic organisms. Only those proteins having functional homologs in thermophilic organisms are most likely to have their thermal stability enhanced. In regard to arguments that the specification makes it clear to one of skill in the art that proteins derived from two or more species correspond to each other when these proteins appear at a similar location in the phylogenic tree designed for each individual species, it is noted that this has not been found persuasive for the reasons already discussed above in Claim Rejections under 35 USC 112, second paragraph in reference to the term "wherein said proteins evolutionarily correspond to each other in a phylogenic tree".

14. It is noted that this rejection may be overcome by including the limitations in claims 19 or 20 in claim 17 and by including the limitations in claims 27 or 28 in claim 23.

15. Claims 17 and 23 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for improving the thermostability of 3-isopropylmalate dehydrogenases and isocitrate dehydrogenases wherein amino acid sequences of 3-isopropyl malate dehydrogenases and isocitrate dehydrogenases from thermophilic bacteria or archaeobacteria are compared, does not reasonably provide enablement for a method for improving thermostability of any protein wherein the amino acid sequences of proteins of similar function or structure from thermophilic bacteria or archaeobacteria are compared. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

16. This rejection has been discussed at length in Paper No. 17 (mailed on 8/26/2003) and Paper No. 12 (mailed on 12/18/2002), and it is applied to amended claims 17 and 23 for the reasons of record and those set forth below.

17. Applicants argue that the claims have been amended to specifically indicate that the phylogenic tree is constructed from proteins isolated from thermophilic organisms as well as the specific algorithm

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used in the construction of the phylogenic tree. Applicants submit that the method can be practice with proteins of different functions in addition to those exemplified in the specification. Applicants direct the Examiner's attention to the summary of the invention and submit that the claims have been amended in accordance to what the Examiner has acknowledged as enabled. Applicants assert that the claims are now fully enabled by the specification and the common ability available in the art.

18. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. The Examiner acknowledges the teachings of the specification and amendments to the claims which now have limitations regarding the nature of the proteins whose amino acid sequences are used in the method, the use of a phylogenic tree, the algorithms used for making the phylogenic tree, and the type of organisms from which some of the proteins used in the construction of the phylogenic tree are isolated. See Claim Rejections under 35 USC 112, second paragraph for claim interpretation. The Examiner agrees that some of the grounds of rejection previously applied in regard to enablement have been overcome with the amendments presented. However, the Examiner disagrees with Applicant's contention that the claims as amended are fully enabled. As indicted above, the claims as amended are still directed to a method for improving thermostability of proteins of any function. As indicated in previous Paper No. 17, in the example provided in the specification and that of the declaration, construction of the phylogenic tree and the ancestral protein required the use of proteins from thermophilic bacteria which have functional homologs in non-thermophilic organisms. Therefore, in both cases, the proteins which had their thermostability enhanced were proteins which had functional homologs in thermophilic organisms. As stated above, only those proteins having functional homologs in thermophilic organisms are most likely to have their thermal stability enhanced. Furthermore, as indicated in the example provided in the specification and the declaration presented, the amino acid sequences used in the construction of the phylogenic tree and the ancestral protein were known in the prior art. Since the scope of the claims encompasses enhancing the thermostability of any protein, it is unclear as to how one can practice the

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claimed method using amino acid sequences which are unknown in the art and are not disclosed in the specification. As discussed at length in Paper No. 12, while one could argue that the amino acid sequences required to practice the claimed method can be isolated by sequence comparison with structures disclosed in the prior art, isolating functional homologs based on structural homology is unpredictable as evidenced by Bork, Broun et al., Seffernick et al. and Van de Loo et al. previously discussed. In view of the information provided, the teachings of the art in regard to the unpredictability of isolating functional homologs based on structural homology, and the lack of knowledge as to which proteins can have their thermal stability enhanced, one cannot reasonably conclude that the specification is fully enabling for the full scope of the claims.

19. It is noted that this rejection may be overcome by including the limitations in claims 19-20 in claim 17 and by including the limitations in claims 27-28 in claim 23.

Claim Rejections - 35 USC § 102

20. Claims 17 and 23 were rejected under 35 U.S.C. 102(b) as being anticipated by Lehmann et al. (Protein Engineering 13(1):49-57, January 2000; cited in the IDS).

21. This rejection has been discussed at length in Paper No. 12, mailed on 12/18/2002, and Paper No. 17 mailed on 8/26/2003.

22. Applicants argue that the claims as amended are free of the disclosure of Lehmann et al.

23. Claims 17 and 23 are now directed to a method for improving thermostability wherein said method uses a phylogenic tree in the design of an ancestral protein, wherein said ancestral protein is then used to determine those amino acids in a protein which if substituted with the corresponding ancestral protein's amino acids may result in a protein with increased thermostability. Since Lehmann et al. does not teach limitations regarding the use of an ancestral protein or a phylogenic tree, this rejection is hereby withdrawn.

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Conclusion

24. No claim is in condition for allowance.


25. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
March 8, 2004


REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP 1600
1600



PIR Frequently Asked Questions

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- **Accession Number:** (1) [What is the difference between an entry code and an accession number?](#) (2) [Why are some accession numbers repeated in different entries?](#)
- **Classification:** (1) [What is meant by "Protein Family", "Protein Superfamily", and "Homology Domain"?](#)
- **Complete Genomes:** (1) [Why are there extra entries for organisms with reported complete genomes?](#) (2) [Why can't I find all the proteins from a recently announced complete genome?](#)
- **Status Tag:** [What do the terms \[validated\], \[similarity\], and \[imported\] in the title mean?](#)
- **Sequence:** [What do the punctuation marks in a protein sequence mean?](#)
- **Database Section:** [What are the different database sections, PIR1, PIR2, PIR3, and PIR4?](#)

Q. Accession Number: (1) What is the difference between an entry code and an accession number? (2) Why are some accession numbers repeated in different entries?

(1) An entry code is the primary unique identifier by which an entry (including sequence and annotations) is identified and retrieved. The entry code appears at the very beginning of the entry. An accession number is a permanent unique identifier that we assign to a sequence when it is imported. PIR accession numbers appear in two places in our entries: individually in the accession block, nested within the reference blocks from which they are derived, and collectively in a single accession line after the date information in each entry.

(2) In the PIR-PSD, we attempt to present the most complete sequence possible for each entry. This frequently becomes a problem with alternatively spliced sequences because the exon sequence in a particular publication may appear out of its genetic context and not include other exon sequences reported elsewhere. In such cases, we must use the same sequence (with the same accession number) in different entries to assemble the complete, different alternative splice forms.

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Q. Classification: What is meant by "Protein Family", "Protein Superfamily", and "Homology Domain"?

Families: For purposes of standardizing annotation, database entries are organized into families of closely related sequences. These generally represent proteins with the same function in various organisms. The taxonomic distribution within a family will depend on how well conserved are the structure and function of the protein. As a general guideline, sequences with more than 50% () sequence identity are usually similar in structure and function and the major sequence features are unambiguously aligned by commonly used multiple sequence alignment programs. Therefore, 50% sequence identity is used by database staff for the provisional clustering of proteins into families. This threshold is appropriate in most cases; however, some families may be repartitioned into more convenient clusters after review.